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SCIENCE MEDICINES HEALTH

Screening for adverse reactions in EudraVigilance

Basel Biometric Society meeting, 29th November 2016

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Disclaimer

Content

Drug-event combination

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Active Substances	SOCs	SMQ Narrow	PTs	IME / DME	New EV	Tot EV	Tot Fatal	AM OM Q	Tot + RC	Tot Lit	Priority Paed	Priority Geriatr	Tot Spontaneous	PRR (-) All	SDR	Priority All	Changes	Signal Status	Comments	Tot Roa (n/a)	Tot Indic. (n/a)
Drug X	Blood		Anaemia		1	127	11	---	0	1			50	0.22			Increased	Closed	20/02/2012.11 valid cases reviewed: 2 cases assessed as non serious, the remaining cases were assessed as unrelated or the causality was not provided because there was always an alternative explanation such as medical history of anaemia, gastric cancer	15	35
Drug X	Blood	Haematopoietic Cytopenias	Leukopenia	Ime	15	522	1	---	8	3			274	3.37	Sdr (33)	2-IME SDR	Increased	Listed	SmPC 4.8	63	166
Drug X	Blood	Haematopoietic Cytopenias	Lymphopenia		28	988	2	---	16	28			548	69.70	Sdr (33)		Increased	Listed	SmPC 4.8	176	361
Drug X	Blood	Agranulocytosis -- Haematopoietic Cytopenias	Pancytopenia	Ime / Dme	1	22	5	---	0	1			15	0.15		1-DME	Increased	Closed	28/01/2014. I review 8 new cases: 2 poorly documented cases, all remaining cases had possible alternative explanations occurring in the context of TEN, UTI, possible meningitis, multiorgan failure and with other co-suspected drugs (i.e. ciclosporin used in the renal transplant indication). 24/01/2013. To be review in the context of the HPS review. 28/06/2012. 6 cases, 4	5	9
Drug X	Blood	Agranulocytosis -- Haematopoietic Cytopenias	Febrile Neutropenia	Ime / Dme	1	5	1	---	0	1			4	0.05		1-DME	Increased	Linked	HPS	0	2
Drug X	Blood	Haematopoietic Cytopenias	Neutropenia	Ime	1	115	0	---	0	0			66	0.46			Increased	Linked	Neutrophil Count Decreased	11	35
Drug X	Blood	Haematopoietic Cytopenias	Thrombocytopenia	Ime	2	72	5	---	1	5			50	0.26			Increased	Closed	Cross refer to HPS:Review new cases. 28/06/2012.15 cases, 10 valid: 2 cases assessed as related to concomitant medications such as carbimazol and chemotherapy, 2 fatal cases, one	8	20

Guidance - Scope

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	Focus	Content	Audience
Screening for Adverse Reactions in EudraVigilance	Evidence based	Rationale of the SD implementation in EV	EU Regulatory Network and MAH

- Focus on what have been **proved** to be effective
  - Approaches presented have been tested and the evidence behind the methods shown
  - Acknowledged where further research may be required
- Input by EU regulatory network experts, research (e.g. PROTECT) and piloting

- Describe the methods of **routine signal detection** as used on EV and clarify the **changes implemented** to increase effectiveness
- Focus on **implementations**
  - Provide some insight into the thinking behind the tools provided for screening EV

Guidance – Main characteristics

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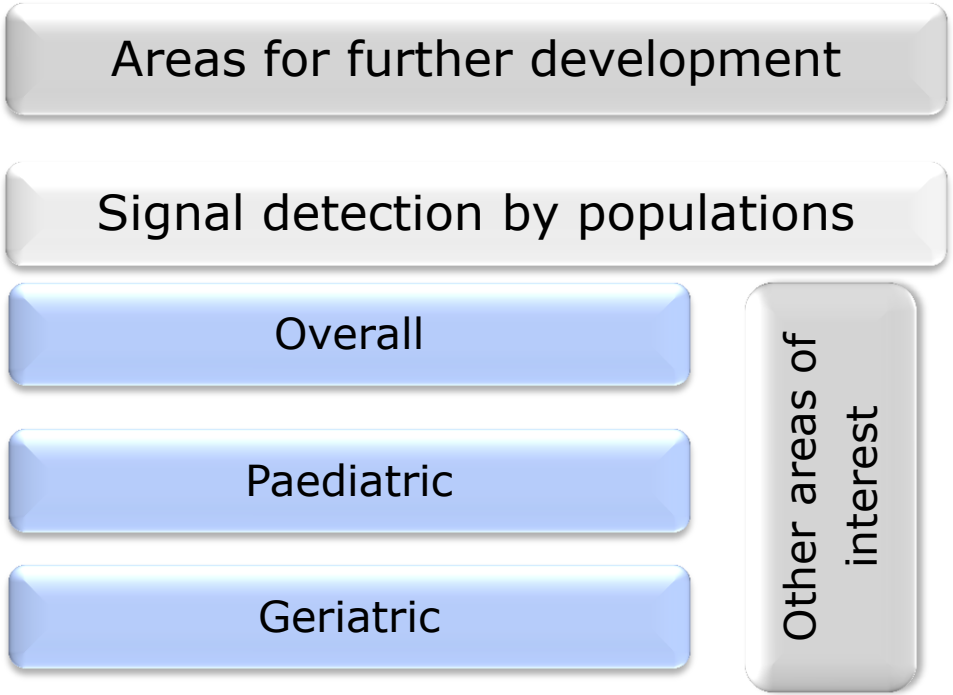
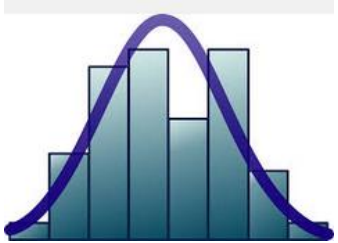
1. Structure



2. Integrated approach

- Proposed approach complements the classical disproportionality analysis with additional data summaries, based on clinical considerations

Disproportionality methods



Clinical methods

Performance

What properties define an effective signal detection system?

- Sensitivity
  - Probability that a known ADR would be detected
- Positive predictive value (PPV or precision)
  - Probability that a DEC highlighted for review identified an ADR
- Time to detection of known ADRs

How do we measure them?

- Reference dataset used to classify true and false positive
  - EMA database that maps section 4.8 of the summary of product characteristics (SPC) for centrally authorised products (CAP) to MedDRA preferred terms (PT) => publicly available
  - For non-CAPs product a dedicated mapping exercise was carried out

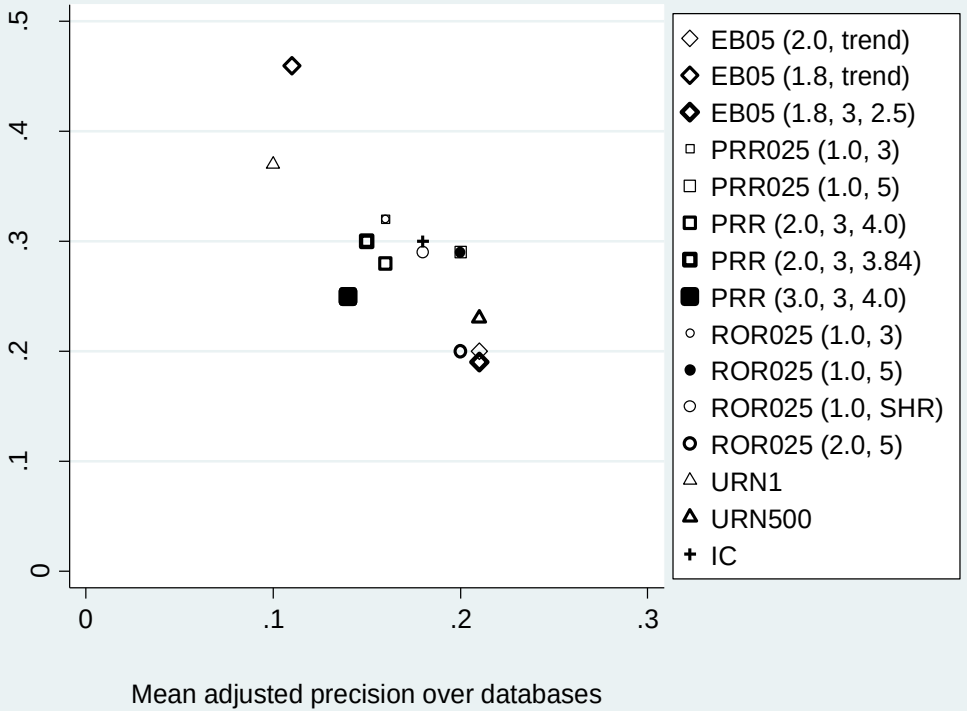
Overall population – Disproportionality methods

Steps in designing a statistical signal detection system

1. Selection of a disproportionality method
2. Thresholds defining SDRs
3. Stratification and subgroup analysis

Overall population – Disproportionality methods

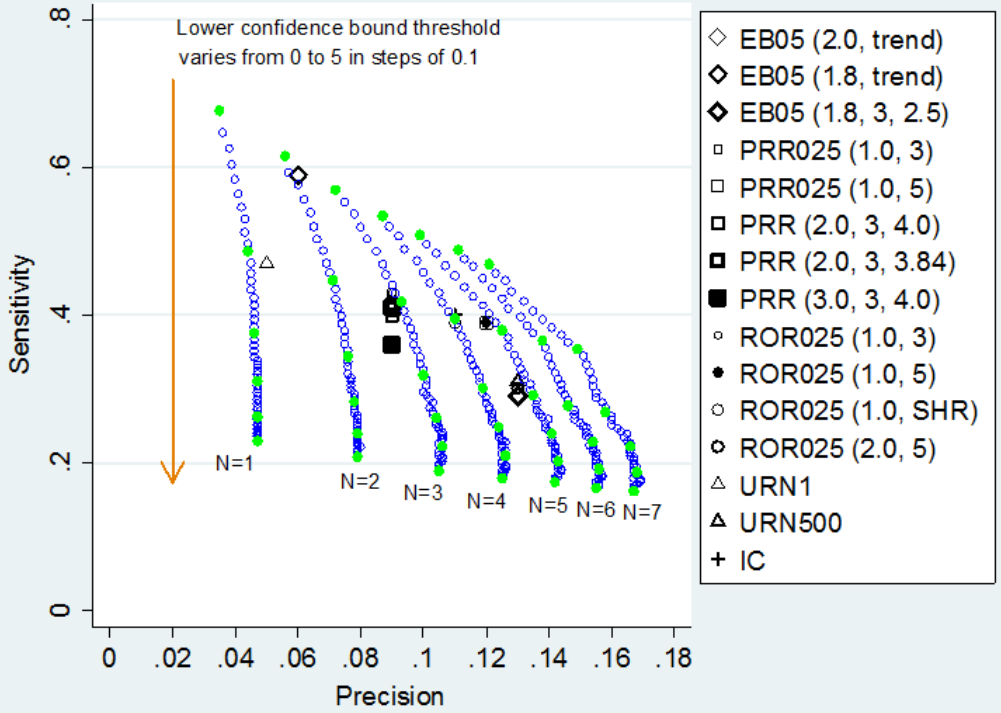
1. Selection of a disproportionality method



Performance averaged over databases to facilitate comparison

- No method falls on the upper-right side
- The largest alterations in performance are produced by changes in the thresholds rather than by the disproportionality statistic

1. Selection of a disproportionality method



- All the methods can be approximated by appropriate choice of thresholds for the ROR
- Choice should be primarily based on ease of implementation, interpretation and minimisation of resources

ROR
(Reporting Odds Ratio)

2. Thresholds defining SDRs

Often based on two separate indicators:

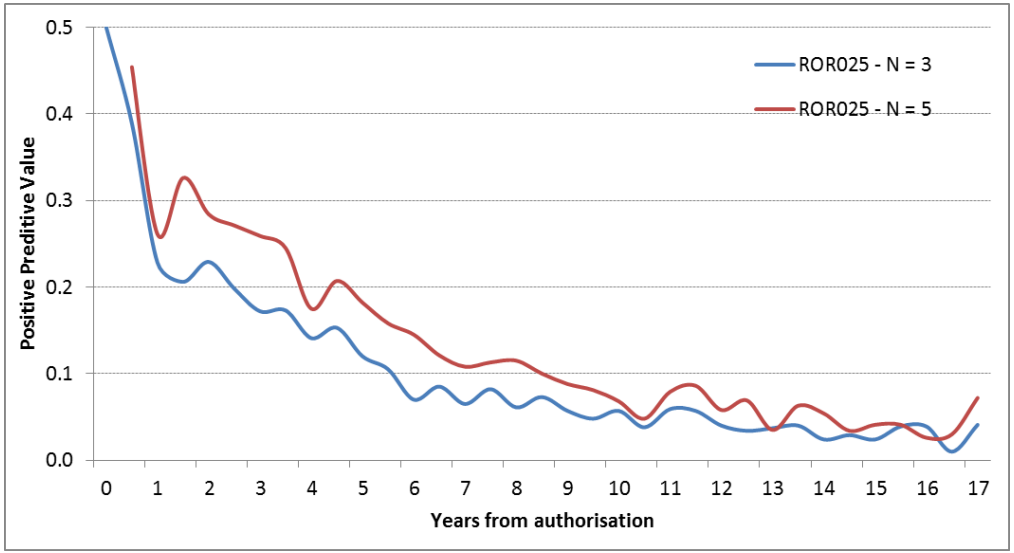
- Lower bound of the 95% confidence interval of the statistics
- Number of reports

What to alter for better efficiency?

- Important Medical Events (IMEs)
- Raising the threshold for the lower confidence bound above 1
  - Appreciable loss of sensitivity with limited reduction of false positive
- Increasing the threshold for the numbers of reports
  - Little loss of sensitivity with greater reduction of false positives

Overall population – Disproportionality methods

2. Thresholds defining SDRs

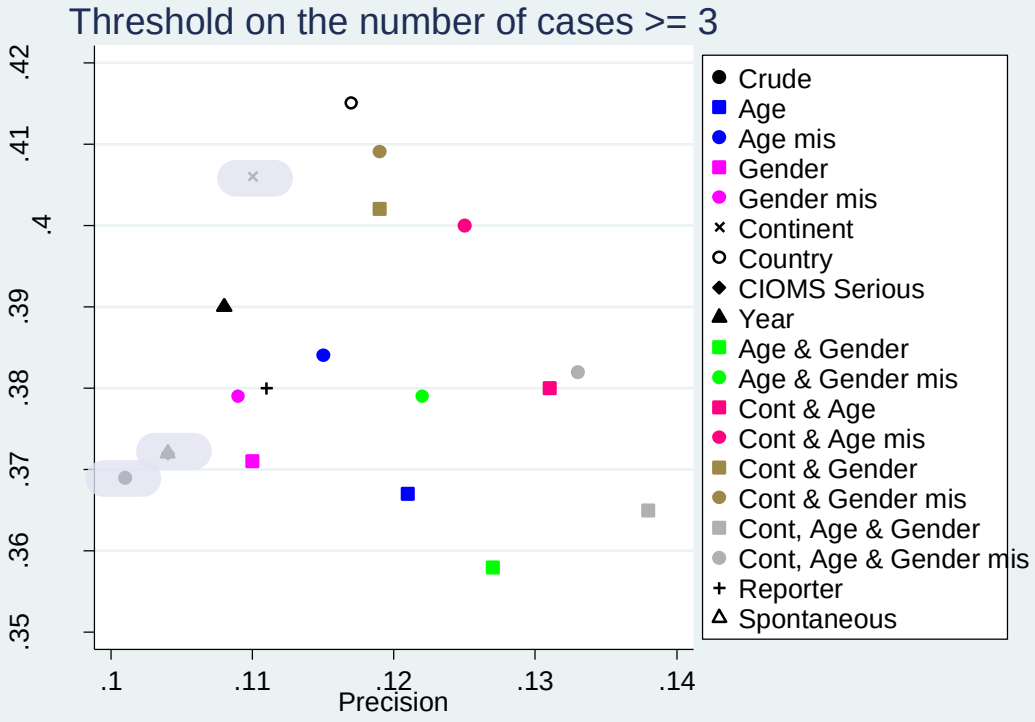


- Fall in precision with time on market
- It might be more efficient to vary the amount of effort invested over the life-cycle of the product

Number of reports:

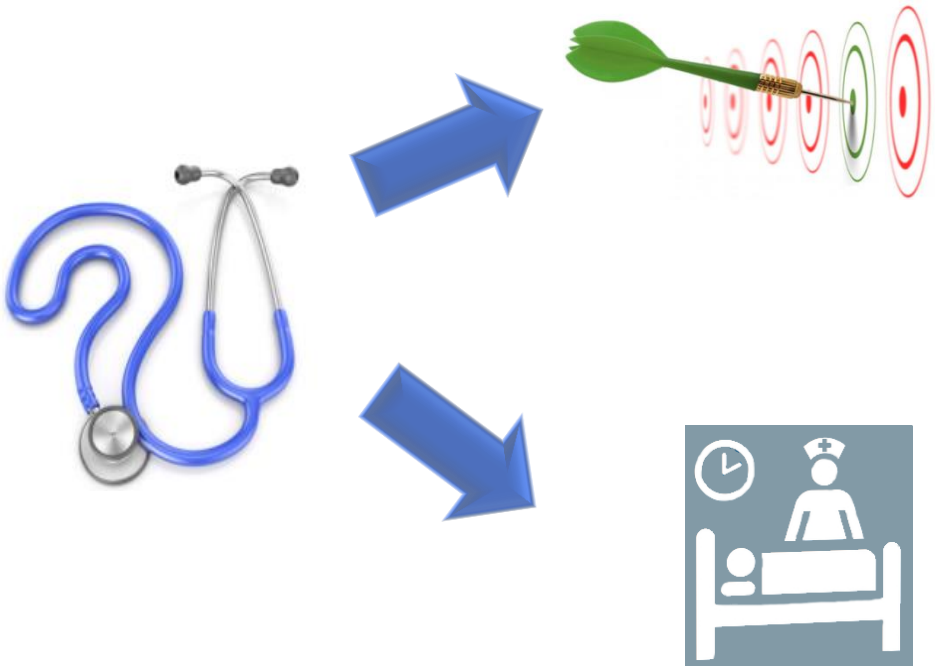
- ≥ 3 for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X)*
- ≥25 for the other active substances

3. Subgroup analysis



- Subgrouping may improve precision and enhance sensitivity
- With threshold on the number of cases >= 5 improvements are smaller
- Exclusion of litigation cases from ROR calculation (still used during signal evaluation)
- Use subgroup by geographical region of reporting

Overall population – Clinical considerations



Designated medical events

- Events known to arise in causal association with medicinal products
- Important and serious events not to be missed

Fatal events (IME)

- May impact the patient and the public health importance

Overall population – Performance

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Performance of disproportionality and additional methods in EV

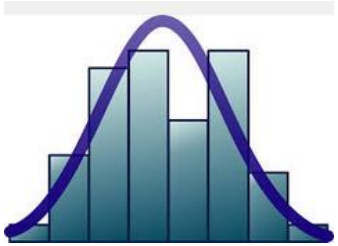
Criteria	Sensitivity	PPV
ROR025 (N=3)	40.6%	11.0%
ROR025 (N=5)	35.6%	15.3%
DME (2016 definition)	19.1%	15.4%
Fatal (IME)	40.9%	5.4%

Performance of additional methods as complement to the SDR in EV

Criteria	Sensitivity	PPV
DME (2016 definition) - with no SDR (N=3)	15.7%	14.4%
DME (2016 definition) - with no SDR (N=5)	15.9%	14.2%
Fatal (IME) - with no SDR (N=3)	11.9%	2.3%
Fatal (IME) - with no SDR (N=5)	13.9%	2.4%

Overall population – Conclusions

Disproportionality methods



Clinical methods

EU Regulatory Network

- DEC highlighted when any of the statistical or clinically based conditions is satisfied
- Information is combined to facilitate the screening for the signal detection validator

Paediatric and geriatric

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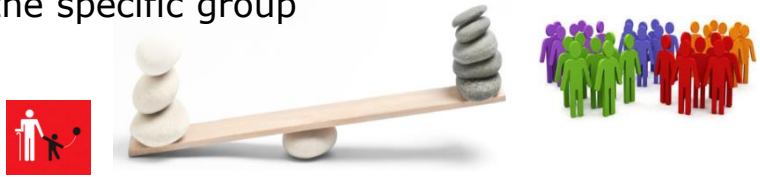
Disproportionality methods

- Same principles as for the overall populations
  - Lower thresholds for paediatric
  - No further subgroups
- Efficiency
  - Focus on disproportionalities more pronounced in the specific group



Relative ROR = ROR $_{\text{specific population}}$ / ROR $_{\text{rest}}$

Clinical considerations*

- Targeted medical events
  - Similar in purpose to the DME
  - Events that have more serious outcomes in children than adults
- Efficiency
  - Terms already flagged as DME are excluded

* Only for the paediatric population and EU regulatory network

Other areas of interest

- Medication error
  - Reports may include information on the circumstances of medicine exposure which could have contributed to the occurrence
  - Knowledge of these circumstances can appreciably alter the assessment of causality

- Positive re-challenge
  - Adverse event reported to have reoccurred after renewed exposure
  - Consistent with a causal relationship

- Literature reports
  - Indicates that more detailed information on the case and additional review of the scientific case for a causal relationship may be available through retrieval of the article that prompted the report

Conclusions

~ 0,5 million Drugs

EudraVigilance

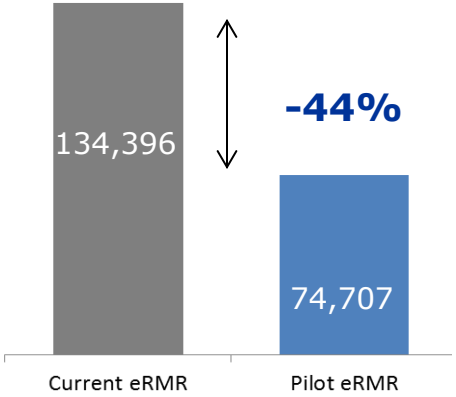
~ 10 millions ICSRs

- These characteristics have influenced the development of signal detection processes in EV
  - Importance of a well-defined process of initial signal detection has increased
  - Focus on efficiency

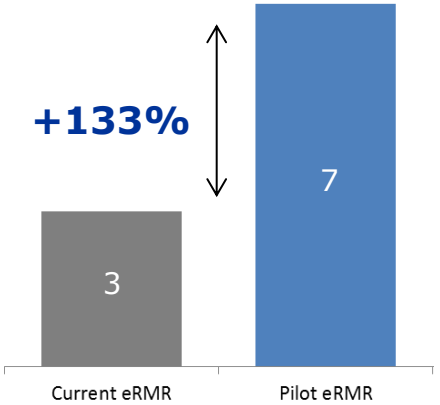
Conclusions

- The recommended methods have the potential to
  - Allow more signals to be detected compared to the previously implemented methodology
  - Without increasing workload

Number of DECs highlighted



Validated signals



- Signal detection is a subject of ongoing research
  - Implementation of a method to detect unexpected increase in frequency is on-going